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A rapid ultrasound-promoted Horner–Wadsworth–Emmons reaction for the preparation of ferrocene derivatives. Application to ferrocene-modified ITO electrodes

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Abstract The Horner–Wadsworth–Emmons reaction of ferrocenecarboxaldehyde with various phosphonate-stabilized carbanions has been performed under ultrasound irradiation. The reaction time at ambient temperature was considerably shortened (5–15 min) compared to nonsonicated conditions requiring often refluxing for 6–24 h. Control of the reaction time can be achieved by tuning the base strength in different solvents. This method was successfully applied to the preparation of various 2-substituted vinylferrocenes. The as-prepared (E)-2-ferrocenylvinylphosphonic acid was used to modify ITO electrodes to form redox-active functionalized ITO electrodes which have been characterized by means of electrochemical techniques.

1. Introduction

Nowadays, ferrocene is considered to be a modular building block in organic synthesis and usually used to introduce a redox-responsive moiety into molecules. Such molecules find many applications in asymmetric catalysis, nonlinear optics, molecular electronic devices, redox polymers and ceramics,

and electrochemical sensors (Atkinson et al., 2004; Bayly et al. 2008). Functionalized ferrocene derivatives can be readily prepared *via* electrophilic substitution by Friedel–Crafts reaction (Dogan et al., 2005; Wang et al., 2008). Since ferrocene displays remarkably a good reactivity toward n-butyl lithium, its subsequent lithiated or boric acid derivatives are excellent starting materials for the preparation of ferrocene derivatives (Sanders et al., 1996; Sato et al., 1971). Among all these compounds, ferrocene carboxaldehyde **1** is probably the most used starting materials for the synthesis of π-conjugated ferrocene-containing systems (Kumar and Swamy, 2001; Shah and Protasiewicz, 1998; Sutcliffe et al., 2001). A ferrocenyl group can be readily introduced into molecules by either Wittig or Horner–Wadsworth–Emmons (HWE) coupling reactions leading to a C=C bond formation. Therefore, 2-substituted

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vinylferrocenes such as alkyl 2-carboxylvinyl ferrocene, 2-cyanovinylferrocene, and 2-ferrocenylvinyl phosphonates (Plazuk et al., 2004; Xia et al., 1995; Kashara et al., 1972; Da Re and Sianesi, 1965; Osgerby and Pauson, 1961) form a series of derivatives bearing terminal groups which can be interconverted into aldehydes, carboxylic acid, phosphonic acids, amines, etc. (Kalvin and Woodard, 1984; Houghton et al., 2010). Moreover, α,β-unsaturated phosphonates of type **2** have been recently reported (Plazuk et al., 2004; Davis et al., 1998), and represent a class of interesting compounds due to their synthetic utility and potential biological activity (Abu Sheikha et al., 2002; Russell, 2011; Davis et al., 1998).

Classical methods for HWE olefination reaction are abundant and a plethora of organic and mineral bases, and Lewis acid metals can be used to form phosphonate-stabilized carbanions ready to react with a large variety of aldehydes and ketones (Marynoff and Reitz, 1989; Ando and Yamada, 2010; Ando and Sato, 2011). The carbanion generation is rapid while the second step often requires longer reaction times and refluxing conditions in high boiling solvents (Rathke and Nowak, 1985). Consequently, it would be interesting to develop faster and cleaner methods for the preparation of such products exploiting ultrasound radiations at room temperature. To our best knowledge there are only two reported cases dealing with the use of ultrasonic irradiation in the HWE olefination (Fuentes et al., 1987; El Fakih et al., 1992). Reaction times were longer and the reaction scope was limited to few carbonyls.

Moreover, indium-doped tin oxide (ITO) films attracted a lot of attention due to their good electrochemical conductivity, high transparency and wide electrochemical working window (Manifacier, 1982) and have been recently employed in different electrochemical applications such as in biosensing (Tam et al., 2008), in displays (Tamara et al., 2013), and in solar cells (Chang et al., 2008). The ITO substrate can be modified or grafted with organic functional group to have tailored materials for specific applications. Das et al. have modified ITO surface with phosphonic acids for the sensitive DNA sensing (Das et al., 2006), while Napier et al. have functionalized it with dicarboxylic acid for the same goal (Napier and Thorp, 1997).

In this work, we report an optimization of the HWE reaction involving ferrocenecarboxaldehyde **1** and various phosphonic acid derivatives under ultrasonic radiation conditions (Scheme 1). The influence of parameters such as base strength, solvent polarity and sonication time on the yield has been investigated. The optimized conditions have been applied for the preparation of a series of 2-substituted vinylferrocenes **2**–**5**. Ferrocenylphosphonic acid, derived from compound **2** prepared under sonochemical conditions, showed promising results for the functionalization ITO electrode.

2. Experimental

2.1. Measurements

The chemicals were purchased from sigma–Aldrich and Acros and used as received. All the solvents used are of analytical grade from LabScan. Thin layer chromatography (TLC) was performed on Fluka aluminum foils pre-coated with F_{254} silica gel. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker Advance 300 MHz apparatus in deuterated solvents as indicated below. Chemical shifts for ^{1}H were reported using TMS signals as internal references. The reaction progress was monitored by TLC or ^{1}H NMR spectroscopy. The ultrasonic irradiation was performed by using a standard commercial cleaning bath operating at a frequency of 35 kHz. Fourier-transform infrared spectra were recorded in ATR mode using a Nicolet 8700 apparatus. The electrochemical experiments were conducted in phosphate saline buffer (PBS, pH = 7.4) solution in a standard three-electrode glass cell using a Metrohm Autolab PGStat M101 electrochemical workstation controlled by Nova 1.8 software. A platinum wire was used as the counter electrode and Ag/AgCl electrode was used as reference electrode. A 2×3 cm ITO-coated glass plate was used as the working electrode. GCMS were recorded on a Perkin–Elmer Autosystem XL GC apparatus (Waltham, MA, USA) equipped with a quadrupole Turbo mass detector. The ionization energy was set à 70 eV.

2.2. ITO electrode modification

ITO-coated glass purchased from SOLEMS (Palaiseau, France) cut into (2×3 cm) rectangular slides was used as a working electrode. The electrode was cleaned by successive ultrasonic treatment in solutions of NaOH (0.1 M), ultrapure water, and ethanol for 20 min. Then, it was rinsed with ultrapure water and sonicated for further 10 min. To modify the ITO electrode with (E)-2-ferrocenylvinylphosphonic acid **2a**, the cleaned ITO electrode was immersed in a 10 mM ferrocenyl vinylphosphonic acid solution for 3 h and sonicated in the same solution for 15 min. The modified ITO electrode was rinsed finally with ultrapure water, dried with N_2 and then used for voltammetric studies.
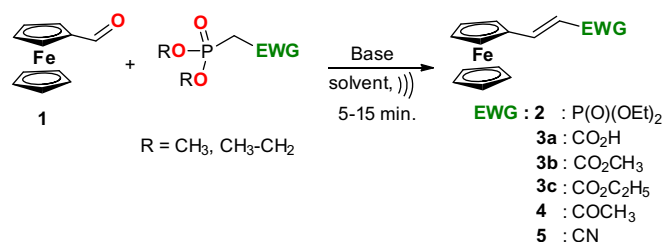
Scheme 1 General route for the preparation of β-substituted vinylferrocenes via a fast ultrasound-assisted Horner–Wadsworth–Emmons reaction.

2.3. General procedure for the ultrasound-assisted reaction

A mixture of ferrocenecarboxaldehyde (54 mg, 0.25 mmol), pastel of sodium hydroxide (70–110 mg, 1.75–4.50 mmol), solvent (1.0 mL), H_2O (0.2 mL, 5 drops) and the desired phosphonate was introduced in a glass vial (volume = 5 mL) and closed with a septum. The sample was irradiated by ultrasound using a Bandelin Sonorex RK25H apparatus operating at 35 kHz (60 W). The bath temperature was maintained at 25–30 °C if not indicated otherwise. The mixture was poured into water and extracted twice with 10 mL of chloroform. The relative yields were determined from the ^1H NMR signal integration. Synthesized products were purified by silica chromatography eluted by (30:70) ethyl acetate/cyclohexane. Compound **2a** was prepared according to the literature from the hydrolysis of diethylphosphonate ester **2** using trimethylchlorosilane followed by treatment in hydrochloric acid (1.0 M) (Plazuk et al., 2004).

2.3.1. Diethyl (E)-ferrocenyl-α,β-unsaturated phosphonate 2

^1H NMR (CDCl$_3$, 300 MHz) δ: 1.28 (6H, t, 3J = 7 Hz, CH$_3$), 4.04 (4H, q, $^3J_{H-H}$ = 7 Hz, CH$_2$), 4.10 (5H, s, Cp), 4.31 (2H, s, C$_\alpha$H-Cp), 4.10 (2H, s, C$_\beta$H-Cp), 5.72 (1H, pseudo t, $^3J_{P-H}$ = 15 Hz, =C$_\beta$H), 7.37 (^1H, dd, $^3J_{P-H}$ = 18 Hz,=C$_\alpha$H) ppm. ^{13}C NMR (CDCl$_3$, 75.5 MHz) δ: 16.1 (s, CH$_3$), 62.3 (s, CH$_2$), 67.9.5 (s, Cp), 69.3 (s, Cp′), 70.4 (s, Cp) 79.4 (s, Cp ipso), 110.7 (s,=C$_\alpha$) δ 149.3 (s,=C$_\beta$). ^{31}P NMR (CDCl$_3$, 121.5 MHz) δ: 20.49 ppm. IR v_{max}: 1607 (C=C), 1244 (P=O), 1019 (P–O–C), 1446, 1244, 1100, 1019 (Cp) cm^{-1}. GCMS: t_R = 38.73 min; m/z = 348 (M$^+$·); 283 (M–C$_5$H$_5$)$^+$; 239 (M–HO–2EtOH)$^+$; 227 (M–FeC$_5$H$_5$)$^+$; 121 (FeC$_5$H$_5$)$^+$.

2.3.2. (E)-2-Ferrocenylvinylphosphonic acid 2a

^1H NMR (CDCl$_3$, 300 MHz) δ: 4.12 (5H, s, Cp), 4.26 (2H, s, C$_\beta$H-Cp), 4.41 (2H, s, C$_\alpha$H-Cp), 5.76 (1H, d, $^3J_{H-H}$ = 15 Hz,=C$_\beta$H), 7.29 (1H, d, $^3J_{H-H}$ = 18 Hz,=C$_\alpha$H) ppm. ^{31}P NMR (methanol-d4) δ: 8.41.

2.3.3. (E)-2-Ferrocenylvinylcarboxylic acid 3a

^1H NMR (CDCl$_3$, 300 MHz) δ: 4.04 (5H, s, Cp), 4.10 (2H, s, C$_\beta$H-Cp), 4.31 (2H, s, C$_\alpha$H-Cp), 6.32 (1H, d, $^3J_{H-H}$ = 15 Hz,=C$_\beta$H), 7.38 (1H, d, $^3J_{H-H}$ = 18 Hz,=C$_\alpha$H) ppm. GCMS: t_R = 31.25 min; 256 (M$^+$·); 254 (M–2H)$^+$; 239 (M–OH)$^+$; 210 (M–2H–CO$_2$)$^+$; 189 (M–2H–FeC$_5$H$_5$)$^+$; 121 (FeC$_5$H$_5$)$^+$.

2.3.4. Ethyl (E)-3-ferrocenylacrylate 3b

^1H NMR (CDCl$_3$, 300 MHz) δ: 1.29 (3H, t, $^3J_{H-H}$ = 7 Hz, CH$_3$), 4.10 (5H, s, Cp), 4.18 (2H, q, $^3J_{H-H}$ = 7 Hz, CH$_2$), 4.36 (2H, s, C$_\alpha$H-Cp), 4.54 (2H, s, C$_\beta$H-Cp), 5.89 (1H, d, $^3J_{H-H}$ = 15 Hz,=C$_\beta$H), 7.52 (1H, d, $^3J_{H-H}$ = 18 Hz,=C$_\alpha$H) ppm. ^{13}C NMR (CDCl$_3$, 75.5 MHz) δ: 14.4 (s, CH$_3$), 60.2 (s, CH$_2$), 68.6 (s, Cp), 69.6 (s, Cp′), 70.1 (s, Cp) 78.8 (s, Cp ipso), 114.7 (s,=Cα), 145.6 (s,=C$_\beta$), 167.3 (s, C=O) ppm. IR v_{max}: 1700 (C=O), 1203 (C–O), 1634 (C=C), 3103 (C=C–H), 2973 (C–H), 1446, 1244, 1103, 1042 (Cp) cm^{-1}. GCMS: t_R = 31.25 min; m/z = 270 (M$^+$); 239 (M–OMe)$^+$; 205 (M–C$_5$H$_5$)$^+$; 175 (M–95)$^+$; 147 (M–123)$^+$; 121 (FeC$_5$H$_5$)$^+$.

2.3.5. Methyl (E)-3-ferrocenylacrylate 3c

^1H NMR (CDCl$_3$, 300 MHz) δ: 3.68 (3H, s), 4.10 (5H, s, Cp), 4.31 (2H, s, C$_\alpha$H-Cp), 4.42 (2H, s, C$_\beta$H-Cp), 5.95 (1H, d, $^3J_{H-H}$ = 9 Hz,=C$_\beta$H), 7.52 (1H, d, $^3J_{H-H}$ = 18 Hz,=C$_\alpha$H). ^{13}C NMR (CDCl$_3$, 75.5 MHz) δ: 51.4 (s, CH$_3$), 68.6 (s, Cp), 69.8(s, Cp′), 71.0 (s, Cp) 78.7 (s, Cp ipso), 114.4 (s,=Cα), 145.9 (s,=Cβ), 167.7 (s, C=O) ppm. IR v_{max}: 1710 (C=O), 1256 (C–O), 1627 (C=C), 3103 (C=C–H), 2984 (C–H), 1448, 1256, 1103, 1052 (Cp) cm^{-1}. GCMS: t_R = 32.64 min, m/z = 284 (M$^+$·); 256 (M–C$_2$H$_4$)$^+$; 239 (M–OEt)$^+$; 219 (M–C$_5$H$_5$)$^+$; 175 (M–109)$^+$; 121 (FeC$_5$H$_5$)$^+$.

2.3.6. (E)-Ferrocenyl-3-buten-2-one 4

^1H NMR (CDCl$_3$, 300 MHz) δ: 2.24 (3H, s, CH$_3$), 4.10 (5H, s, Cp), 4.40 (2H, s, C$_\alpha$H-Cp), 4.44 (2H, s, C$_\beta$H-Cp), 6.28 (1H, d, $^3J_{H-H}$ = 15 Hz,=C$_\beta$H) 7.38 (1H, d, $^3J_{H-H}$ = 15 Hz,=C$_\alpha$H). ^{13}C NMR (CDCl$_3$, 75.5 MHz) δ: 27.2 (s, CH$_3$), 68.8 (s, Cp), 69.7 (s, Cp′), 71.2 (s, Cp), 78.6 (s, Cp ipso), 124.7 (s,=C$_\alpha$), 145.1 (s,=C$_\beta$), 197.8 (s, C=O) ppm. IR v_{max}: 1651 (C=O), 1614 (C=C), 3103 (C=C–H), 2964 (C–H), 1446, 1258, 1104, 1043 (Cp) cm^{-1}. GCMS: t_R = 30.9 min, m/z = 254 (M$^+$·); 189 (M–C$_5$H$_5$)$^+$; 121 (FeC$_5$H$_5$)$^+$.

2.3.7. (E)-3-Ferrocenylacryloyl cyanide 5

^1H NMR (CDCl$_3$, 300 MHz) δ: 4.10 (5H, s, Cp), 4.40 (4H, s, Cp), 5.35 (1H, d, $^3J_{H-H}$ = 9 Hz,=C$_\beta$H), 7.20 (1H, d, $^3J_{H-H}$ = 12 Hz,=C$_\alpha$H) ppm. ^{13}C NMR (CDCl$_3$, 75.5 MHz) δ: 68.7 (s, Cp), 69.9 (s, Cp′), 71.4 (s, Cp), 78.1 (s, Cp ipso), 91.8 (s,=Cα), 119.1 (s, C≡N), 151.5 (s,=Cβ) ppm. IR v_{max}: 2206 (C≡N), 1608 (C=C), 2961 (C–H), 1456, 1259, 1101, 1043 (Cp) cm^{-1}. GCMS: t_R = 28.0 min, m/z = 237 (M$^+$·); 172 (M–C$_5$H$_5$)$^+$; 121 (FeC$_5$H$_5$)$^+$.

3. Results and discussion

3.1. Base and solvent effects

Preliminary investigations showed that sonication of a mixture of ferrocenecarboxaldehyde **1** and methylene bis(diethyl-phosphonate) in a given solvent afforded diethyl 2-ferrocenyl-α, β-unsaturated phosphonate **2** in few minutes (5–15 min). However, the same mixture of reagents gives the correspondent product with 30% of yield using heating mode and under stirring for 24 h. The unreacted aldehyde **1** can be easily recovered using separation by silica column chromatography eluted by ethyl acetate/cyclohexane (30:70). Moreover, the reaction progress can be easily monitored by TLC or ^1H NMR spectroscopy. Aldehyde **1** was reacted with methylene bis(diethyl-phosphonate) in the presence of a base affording compound **2** according to Scheme 1. A small amount of water was systematically added to dissolve the mineral bases. The bath temperature was kept at ambient temperature by addition of cold water if it rises above 30 °C. The influence of solvent and base was systematically studied and the results are reported in Table 1. The relative yields of product **2** were determined from the ratio of the integrated ^1H NMR signal of the remaining carbonyl proton of the aldehyde **1** and the α,β vinylic protons of the product **2**. All the products were obtained exclusively as (E)-isomers which has been confirmed by comparing ^1H NMR spectra with the literature data (Davis et al., 1998; Plazuk et al., 2004).

Table 1 Relative yields of product **2** obtained from the reaction of ferrocenecarboxaldehyde **1** with 4 equiv. of methylene bis(diethyl-phosphonate) in presence of bases (4.8 equiv.) in various solvents under ultrasonic irradiation at ambient temperature.

Entry	Solvent[a]	Base	Time (min)[b]	**1** (%)	**2** (%)[c]
1	THF	No	180	>99	–[d]
2		NaHCO$_3$	60	>99	–[d]
3		Na$_2$CO$_3$	45	>99	–[d]
4		K$_2$CO$_3$	45	91	9
5		K$_2$CO$_3$	90	85	15
6		Et$_3$N	90	>99	–[d]
7		NaOH	15	–[d]	>99
8		LiOH	07	29	71
9		LiOH	15	–[d]	>99
10		KOH	30	49	51
11		KOH	60	21	79
12		tBuONa	30	58	42
13		tBuOK	30	71	29
14		tBuOK	90	32	68
15	ACN	KOH	30	<30	>70
16		NaOH	15	<30	>70
17		NaOH	30	<20	>80
18	DMF	KOH	30	85	>15
19		NaOH	15	–[d]	>97
20	DMSO	KOH	30	>90	>10
21		NaOH	15	<20	>80
22		NaOH	30	<10	>90
23		NaOH	45	–[d]	>95
24	tBuOH	NaOH	30	>40	60
25		NaOH	45	–[d]	>95
26	H$_2$O	KOH	15	81	19
27		NaOH	05	4	96
28		NaOH	15	–[d]	>99

[a] 1 mL of solvent and 250 μL of H$_2$O to dissolve the mineral base (80:20).
[b] Time of ultrasonic irradiation.
[c] Yield of the formed product for 1H NMR signal integration.
[d] ^{1}H NMR signals of **1** or **2** are not measurable.

In THF and in absence of a base, no conversion of compound **1** was observed even after 180 min of ultrasonic irradiation (Table 1, entry 1). Weak bases such as sodium bicarbonate or sodium carbonate or organic bases such as triethylamine did not yield any HWE products. The starting aldehyde **1** was entirely recovered (entry 2–3, 6). When potassium bicarbonate is used, the yields are still low and do not exceed 15% after 90 min (entry 4–5). For stronger bases such as alkali hydroxides, the yields of **2** were significantly improved (entry 7–11). For instance, a total consumption of the aldehyde and formation of **2** in yields >99% were obtained after 15 min of sonication using NaOH or LiOH and the aldehyde proton signal was no longer detectable in the ^{1}H NMR spectra. However, when KOH was used, the transformation was still unfinished after 1 h of irradiation suggesting an effect of the metallic cation in the stabilization of the anionic intermediate (Thompson and Heathcook, 1990). After 30 min of irradiation with stronger bases such as tBuONa or tBuOK, the reaction was not complete (entry 12–13). In the water-containing reaction mixture, the tert-butyl alcoholates are converted into the corresponding alcohols rendering the solution highly viscous what is probably the reason for the lower yields of **2**.

In acetonitrile (ACN), dimethylformamide (DMF), dimethylsulfoxide (DMSO), tert-butanol (tBuOH) or H$_2$O as solvents, sodium hydroxide gives always better results than potassium hydroxide and the yields in these solvents are lower than those obtained in THF or in water (entry 15–28). A combination of THF/H$_2$O–NaOH or H$_2$O–NaOH seems to be the best choice for this reaction (entry 7 and 27–28).

3.2. Effects of ratio of reagents and sonication time

The reaction rate also depends on the ratio of aldehyde and phosphonate, and the sonication time (Table 2). In fact, for 1.2 equiv. of bisphosphonate (EWG = (EtO)$_2$P(O)) dissolved in THF, irradiation for 30 min gave product **2** in yields of 90% (entry 1–2). In the presence of 2.0 equiv. of bisphosphonate, conversion of **1** was faster and product **2** was obtained in 81% after 15 min of irradiation, and the reaction was almost complete after 30 min (entry 3–4). Using a threefold to sevenfold excess of bisphosphonate, the yields increased to 83% and more than 99% after 15 min of sonication, respectively (entry 5–7). For the same duration in water, only 2 equiv. of bisphosphonate were needed for a complete conversion (entry

Table 2 Effect of the solvent and the ratio of methylene bis(diethylphosphonate) and aldehyde on the reaction yield under ultrasonic irradiation at ambient temperature in presence of NaOH (1.2 equiv).[a]

Entry	Solvent	Phosphonate	Time (min)	1 (%)[c]	2 (%)[c]
1	THF[b]	1.2	15	77	23
2		1.2	30	10	90
3		2.0	15	19	81
4		2.0	30	04	96
5		3.0	15	17	83
6		4.0	15	–	> 98
7		7.0	15	–	> 99
8	H_2O	1.2	15	52	48
9		1.2	30	45	55
10		1.2	45	29	71
11		2.0	15	–	> 98

[a] In respect of bisphosphonate.
[b] THF/H_2O (80/20).
[c] Relative yields determined from ^1H NMR titration.

8–11) denoting strong effect of the solvent polarity on the reaction rate (Thompson and Heathcook, 1990).

3.3. Preparation of 2-substituted vinylferrocenes

The optimal conditions (THF/H_2O–NaOH) have been successfully applied to the preparation of a series of 2-substituted vinylferrocenes **2–5** where EWG = P(O)(OEt)$_2$, CO$_2$H, CO$_2$-Et, CO$_2$Me, COCH$_3$ and CN. Starting from the appropriate dialkyl phosphonate, ultrasonic irradiation in presence of sodium hydroxide in THF or in H_2O afforded the desired products (Table 3). In case of products **3b/c** (EWG = CO$_2$R), when a large excess of sodium hydroxide in water was used (*ca.* 11 equiv.), the formed products **3b** and **3c** were not isolated but they were hydrolyzed *in situ* to their corresponding acid **3a** (entry 4, 5). A 4–8 fold excess gave the vinylferrocenes **2–5** in excellent yields. In the case of product **3c** using THF/H_2O as

solvent and after 15 min of sonication, the yield was only of 72% with the recovery of ∼30% aldehyde. Using only THF did not improve the yields (entry 8–9). Rathke et al. reported that the addition of a chelating cation such Li$^+$ or Mg^{2+} ameliorated the reaction yields by stabilizing the carbanions (Rathke and Nowak, 1985). Addition as LiClO$_4$ did not improve much the yields but when anhydrous magnesium sulfate was added, the reaction was complete in less than 5 min (entry 8, 10–11). A general procedure was established and the compounds **2–5** were characterized by ^1H NMR spectroscopy and GC–MS confirming already published results.

3.4. Modification of ITO electrode

Recently, it was demonstrated that the modification of ITO substrates by self-assembled monolayers (SAMs) of electroactive molecules or oligomers, bearing a terminal phosphonic

Table 3 Relative yield products **2–5** from the reaction between ferrocenecarboxaldehyde **1** and **4** equivalents of phosphonate-stabilized carbanions under ultrasonic irradiation at ambient temperature.

Entry	Phosphonate	Conditions	Time (min)	Products	Yield (%)	1 (%)
1	(EtO)$_2$P(O)CH$_2$P(O)(OEt)$_2$	LiOH (4.0 equiv.)[a,d]	07	**2**: Fc-CH=CH—P(O)(OEt)$_2$	72	28
2	(EtO)$_2$P(O)CH$_2$P(O)(OEt)$_2$	LiOH (4.0 equiv.)[a,d]	15	**2**: Fc-CH=CH—P(O)(OEt)$_2$	> 99	–[g]
3	(EtO)$_2$P(O)CH$_2$P(O)(OEt)$_2$	NaOH (7.0 equiv.)[b,d]	15	**2**: Fc-CH=CH-P(O)(OEt)$_2$	> 99	–[g]
4	(EtO)$_2$P(O)CH$_2$CO$_2$Et	NaOH (11.0 equiv.)[c]	15	**3a**: Fc-CH=CH-CO$_2$H	84	16
5	(MeO)$_2$P(O)CH$_2$CO$_2$Me	NaOH (11.0 equiv.)[c]	15	**3a**: Fc-CH=CH—CO$_2$H	51	49
6	(EtO)$_2$P(O)CH$_2$CO$_2$Et	NaOH (7.0 equiv.)[a]	15	**3b**: Fc-CH=CH—CO$_2$Et	60	40
7	(EtO)$_2$P(O)CH$_2$CO$_2$Et	NaOH (7.0 equiv.)[d]	05	**3b**: Fc-CH=CH—CO$_2$Et	> 99	–[g]
8	(MeO)$_2$P(O)CH$_2$CO$_2$Me	NaOH (7.0 equiv.)[a]	15	**3c**: Fc-CH=CH-CO$_2$Me	72	28
9	(MeO)$_2$P(O)CH$_2$CO$_2$Me	NaOH (7.0 equiv.)[d]	15	**3c**: Fc-CH=CH—CO$_2$Me	74	26
10	(MeO)$_2$P(O)CH$_2$CO$_2$Me	NaOH (7.0 equiv.)[e]	15	**3c**: Fc-CH=CH—CO$_2$Me	73	27
11	(MeO)$_2$P(O)CH$_2$CO$_2$Me	NaOH (7.0 equiv.)[f]	05	**3c**: Fc-CH=CH—CO$_2$Me	> 99	–[g]
12	(EtO)$_2$P(O)CH$_2$COCH$_3$	NaOH (7.0 equiv.)[d]	05	**4**: Fc-CH=CH—COCH$_3$	> 99	–[g]
13	(EtO)$_2$P(O)CH$_2$CN	NaOH (7.0 equiv.)[d]	05	**5**: Fc-CH=CH—CN	> 99	–[g]

[a] Solvent: THF/H_2O (80/20).
[b] Solvent can be either H_2O or THF/H_2O.
[c] Solvent: H_2O only.
[d] Solvent: THF only.
[e] 8 equiv. of LiClO$_4$ were added.
[f] 8 equiv. of anhydrous MgSO$_4$ were added.
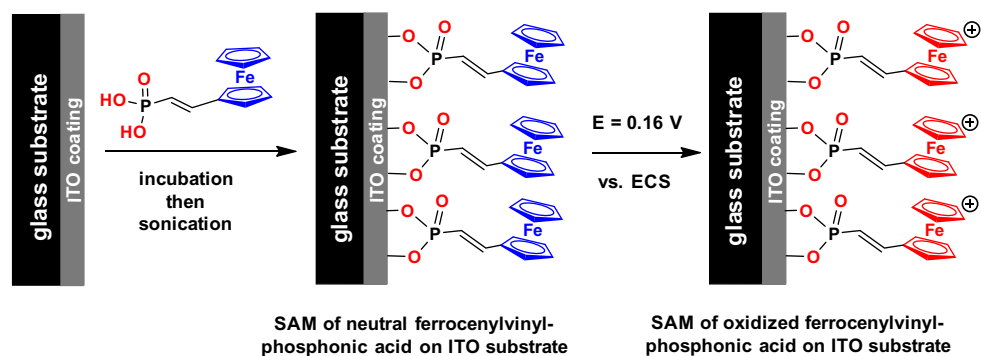[g] ^1H NMR signals of Fc-CHO are not measurable.

Figure 1 Schematic representation of the adsorption process of the ferrocenylvinylphosphonic acid and the oxidation of ferrocene-modified SAM on the ITO electrode.

group (R-P(O)(OH)$_2$), can be used in optical devices such as polymer light-emitting diodes (PLEDs). The SAMs showed great promises in maximizing the injection of holes into conducting photoactive oligomers and polymers (Hanson et al., 2005; Bardecker et al., 2008). The (E)-2-ferrocenylvinylphosphonic acid **2a** was chosen thanks to the good affinity of the

phosphonic acid group to ITO substrates (Chockalingam et al., 2011). Before immobilizing the ferrocenylphosphonic acid **3a** onto ITO electrode surfaces, the bare electrode was pretreated by a sequential cleaning with NaOH, EtOH and ultrapure water. The electrode was then immersed for 3 h and sonicated for 15 min in a diluted ferrocenic solution and
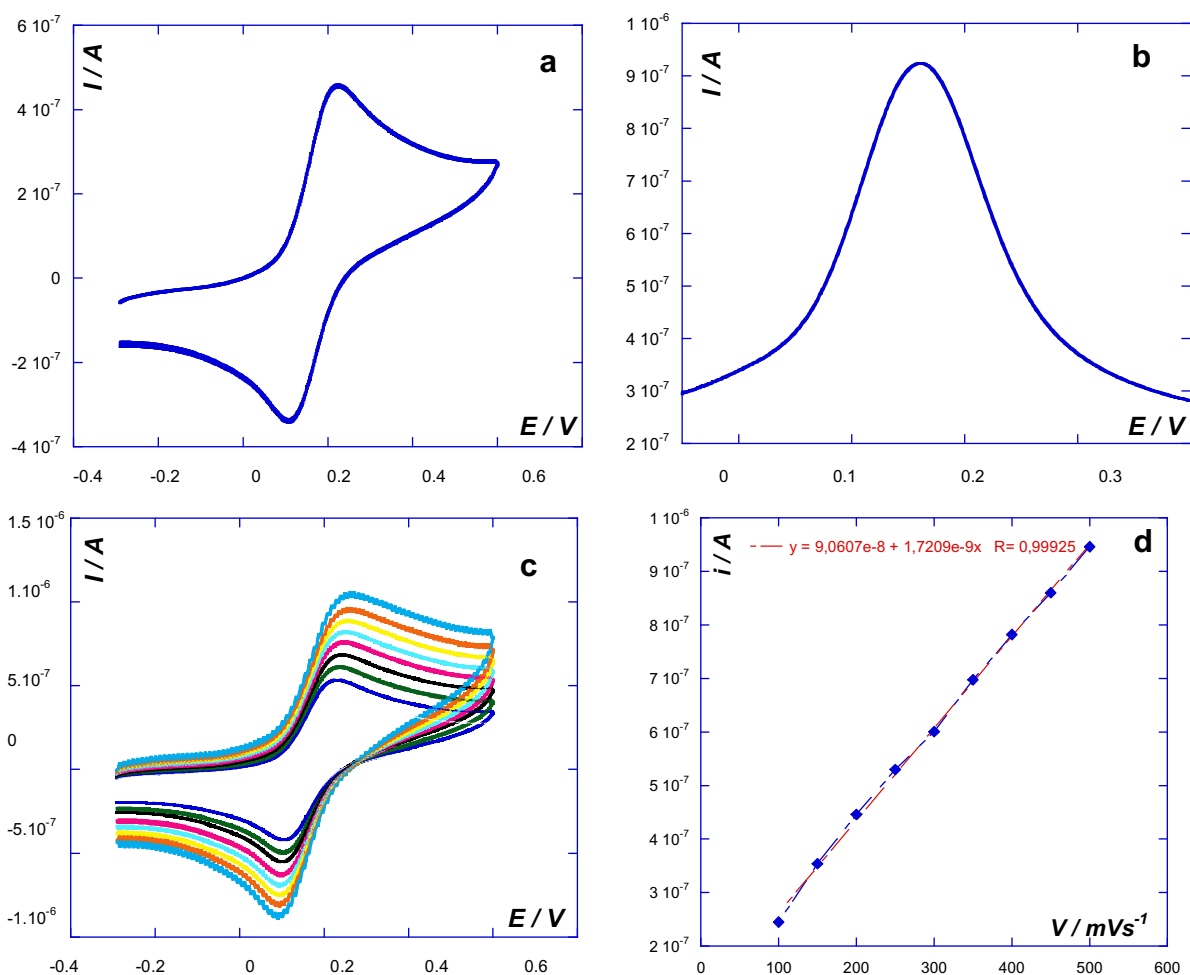

Figure 2 (a) Cyclic voltammetry recorded at 100 mV/s in a PBS solution of the ferrocene-modified ITO electrode (working electrode), Ag/AgCl (KCl 3 M) as reference electrode and a platinum wire as counter electrode, (b) DPV performed in PBS using the previous three electrodes as electrochemical device, (c) cyclic voltammetry at various scan rates from 100 to 500 mV s^{-1}, (d) Randles–Sevick plot of oxidation peak current versus the scan rates.

thoroughly washed with ethanol then water to remove non-bonded molecules (Fig. 1).

Cyclic voltammetry (CV), performed in a PBS solution, displayed a quasi-reversible signal (i_{pc}-to-i_{pa} ratio close to unity and peak-to-peak separation is close to 60 mV) related to a one electron transfer from the ferrocene moiety which is oxidized to a ferrocenium cation (Fig. 2a). The DPV curve of the ferrocene-modified ITO electrode as a working electrode marks the presence of an oxidation signal localized at 0.16 V which is related to the presence of ferrocenic group confined on ITO electrode surface (Fig. 2b). To assess the presence of the ferrocene binding the ITO, several CVs at various scan rates from 100 to 500 mV s^{-1} were performed and are displayed in Fig. 2c. The Randles–Sevick plot representing the oxidation current peak versus the scan rate showed a linear relationship suggesting an adsorption-controlled electrode process according to plot (Fig. 2d) (Li et al., 2008; Sahli et al., 2013) and thus proving that the electroactive molecules are confined to the electrode surface. Moreover, these redox wave shapes did not change during continuous potential cycling over several hundred of cycles at room temperature confirming the stability of SAMs.

4. Conclusion

Compared to the classical HWE reaction conditions, the ultrasound-assisted reaction of ferrocene carboxaldehyde with various activated methylene phosphonates was considerably accelerated by ultrasonic irradiation using a simple ultrasonic cleaning bath. Sodium hydroxide/aqueous THF or sodium hydroxide/H$_2$O solutions were found to give fast conversions (5–15 min) at room temperature. This methodology has been successfully applied to the preparation of a series of 2-substituted vinylferrocenes, all useful precursors in the synthesis of ferrocene derivatives. The as-synthesized ferrocenyl vinylphosphonic acid was found to be a useful compound to form a SAM on the ITO surface as verified by means of electrochemical measurements. The later one can serve as a platform for the development of the sensitive biosensors.

Acknowledgments

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.arabjc.2014.11.049.

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